

What Is Claimed Is:

1. A stable and taste masked pharmaceutical dosage form comprising porous apatite grains and a drug entrapped in pores of said grains, wherein said grains have a size of 0.1-1000 μm and said pores of said grains have an opening
5 of 0.5-300 nm.

2. The pharmaceutical dosage form according to claim 1 further comprising a water soluble polymer entrapped in pores of said grains in an amount of 0.1-10% based on the weight of the grains.
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3. The pharmaceutical dosage form according to claim 1, wherein said grains have a size of 1 to 300 μm .

4. The pharmaceutical dosage form according to claim 1, wherein said
15 pores have an opening of 1 to 200 nm.

5. The pharmaceutical dosage form according to claim 1, wherein said grains have a specific surface area of 32 to 58 m^2 per unit gram.

20 6. The pharmaceutical dosage form according to claim 1, wherein said drug entrapped in said porous apatite grains is in an amount of 0.1-45% based on the weight of the grains.

7. The pharmaceutical dosage form according to claim 6, wherein said
25 drug entrapped in said porous apatite grains is in an amount of 1-30% based on the weight of the grains.

8. The pharmaceutical dosage form according to claim 2, wherein said water soluble polymer is selected from the group consisting of chitosan, gelatin, agar, cellulose, chitin, starch, dextrin, cyclodextrin, polylactic acid, polyamino
30 acid, polyethylene glycol, polyacrylates, hyaluronic acid, polyvinyl alcohol, povidone and mixture thereof.

9. The pharmaceutical dosage form according to claim 8, wherein said water soluble polymer is cellulose, polyethylene glycol, polyvinyl alcohol, or povidone.

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10. The pharmaceutical dosage form according to claim 1, wherein said apatite grains have a Ca to P molar ratio of 1.1 to 2.1.

11. The pharmaceutical dosage form according to claim 10, wherein said
10 apatite grains have a Ca to P molar ratio of 1.3 to 1.60.

12. The pharmaceutical dosage form according to claim 1, wherein said apatite grains contains carbonate in an amount of 0.1-40% based on the weight of the grains.

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13. The pharmaceutical dosage form according to claim 12, wherein said apatite grains have a Ca to P molar ratio of 1.3 to 1.60.

14. The pharmaceutical dosage form according to claim 1, wherein said
20 drug is a peptide, protein, enzyme, DNA, RNA, nutrient supplement agent, anti-inflammatory drug, anti-biotic drug, anti-histamine drug, anti-bacterial drug, anti-fungal drug, decongestant, anti-depressant, anti-psychotic drug, anti-viral drug, anti-oncolytic drug, vaccine, anti-epileptic drug, anti-asthma drug, antioxidant or extract of herb.

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15. The pharmaceutical dosage form according to claim 1, wherein said drug is selected from a group of zinc gluconate, copper gluconate, carbinoxzmine maleate, dextromethorphan hydrobromide, glyceryl guaiacolate, pseudoephedrine hydrochloride, triprolidrine hydrochloride, acetaminophen, aspirin, ibuprophen,
30 dexibuprophen lysinate, naproxen, ketoprofen, lactam, quinolone, macrolide or salts thereof, loperamide, famotidine, ranitidine, cimetidine or salts thereof, ibersartan, captopril, lisinopril or salts thereof, nefzodone, buspirone or salts

thereof, chlorpheniramine, astemizole, pseudoephedrine, medicon, anpirin, actirin, nidolin, ascorbic acid, hydrocortisone, 5-fluorouracil, cis-platin, paclitaxel, ampicilin, cefadroxil, clindamycin, neomycin, nystatin, polyphenol, hydroquinone, and retinal A.

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16. The pharmaceutical dosage form according to claim 15, wherein said drug is zinc gluconate, copper gluconate, aspirin, ibuprophen or ascorbic acid.

17. The pharmaceutical dosage form according to claim 1 further
10 comprising a biocompatible polymer, and said porous apatite grains are bound by said biocompatible polymer to form a microspherical composite having a size of 0.5-1000 μm .

18. The pharmaceutical dosage form according to claim 17, wherein said
15 biocompatible polymer is in an amount of 0.5% to 30% based on the weight of the grains.

19. The pharmaceutical dosage form according to claim 17, wherein said biocompatible polymer is selected from the group consisting of polylactic acid,
20 polyglycolic acid, poly(lactic-co-glycolic acid), polyanhydrides, polyethylene glycol, polyethylene oxide, polyacrylates, polymethacrylates, dextran, polysaccharides, hyaluronic acid, and mixture thereof.

20. The pharmaceutical dosage form according to claim 19, wherein said
25 biocompatible polymer is polylactic acid, polyethylene glycol, or poly(lactic-co-glycolic acid).

21. A process for preparing a stable and taste masked pharmaceutical dosage form comprising the following steps:

30 a) mixing particles of a calcium source and particles of a phosphate source in a non-aqueous liquid medium, and optionally milling the resulting mixture, so

that a slurry has a Ca/P ratio of 1.1-2.1 and particles suspended therein having a size of 0.01-20 μm ;

b) adding a drug soluble in said non-aqueous liquid medium to the slurry;

c) granulating the slurry;

5 d) adding an aqueous solution of a drug or a drug-free aqueous solution to the resulting granules from step c);

e) stirring or fluidizing the wetted granules, so that porous apatite grains are formed, wherein said drug is entrapped in pores of said grains, wherein said grains has a size of 0.1-1000 μm and said pores of said grain have an opening of
10 0.5-300 nm,

wherein step b) may be omitted, when said aqueous solution of the drug in step d) is added to the resulting granules from step c).

22. The process according to claim 21, wherein step a) further comprises
15 mixing particles of carbonate source together with said particles of calcium source and phosphate source in an amount of 0.1-40% based on the total weight of said particles of calcium source and phosphate source.

23. The process according to claim 21, wherein said non-aqueous liquid
20 medium in step a) selected from the group consisting of methanol, ethanol, 1-propanol, 2-propanol, acetone, methyl ethyl ketone, toluene, ethyl acetate, butyl acetate, and a mixture thereof.

24. The process according to claim 21, wherein said phosphate source in
25 step a) is selected from the group consisting of magnesium phosphate, monocalcium phosphate anhydrate, dicalcium phosphate anhydrate, tricalcium phosphate, potassium dihydrogen phosphate, sodium dihydrogen phosphate, and a combination thereof.

30 25. The process according to claim 21, wherein said calcium source in step a) is selected from the group consisting of calcium hydroxide, calcium chloride, calcium carbonate, and a combination thereof.

26. The process according to claim 22, wherein said carbonate source in step a) is selected from the group consisting of calcium bicarbonate or sodium bicarbonate or potassium bicarbonate, and a combination thereof.

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27. The process according to claim 21, wherein the mixture of particles of the calcium source and the phosphate source has a Ca to P molar ratio of 1.1 to 2.1.

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28. The process according to claim 27, wherein the mixture of particles of the calcium source and the phosphate source has a Ca to P molar ratio of 1.3 to 1.60.

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29. The process according to claim 22, wherein the mixture of particles of the calcium source and the phosphate source has a Ca to P molar ratio of 1.3 to 1.60.

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30. The process according to claim 21, wherein said drug in step b) and said drug in step d) are in an amount of 0.1-45% based on the weight of the grains formed in step e).

31. The process according to claim 21, wherein said granulating in step c) comprises atomizing said slurry and drying the resulting aerosol.

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32. The process according to claim 21, wherein said aqueous solution of the drug in step d) is sprayed to the resulting granules from step c), while stirring or fluidizing.

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33. The process according to claim 21, wherein said drug-free aqueous solution in step d) is sprayed to the resulting granules from step c), while stirring or fluidizing, wherein said drug-free aqueous solution is water, phosphate buffered aqueous solution, or Hank's solution.

34. The process according to claim 21, wherein water contained in said aqueous solution of the drug and said drug-free aqueous solution in step d) added to the resulting granules from step c) is in a weight ratio of said water to the
5 mixture of particles of the calcium source and the phosphate source of 0.05:1 to 0.30:1.

35. The process according to claim 22, wherein water contained in said aqueous solution of the drug and said drug-free aqueous solution in step d) added
10 to the resulting granules from step c) is in a weight ratio of said water to said mixture of particles of calcium source, phosphate source and carbonate source of 0.05:1 to 0.30:1.

36. The process according to claim 21, wherein said aqueous solution of
15 the drug and said drug-free aqueous solution in step d) further comprises a water soluble polymer in an amount of 0.1-10% based on the weight of the mixture of particles of the calcium source and the phosphate source.

37. The process according to claim 36, wherein said water soluble
20 polymer is selected from the group consisting of chitosan, gelatin, agar, cellulose, chitin, starch, dextrin, cyclodextrin, polylactic acid, polyamino acid, polyethylene glycol, polyacrylates, hyaluronic acid, polyvinyl alcohol, povidone and mixture thereof.

25 38. The process according to claim 37, wherein said water soluble polymer is cellulose, polyethylene glycol, polyvinyl alcohol, or povidone.

39. The process according to claim 22, wherein said aqueous solution of the drug and said drug-free aqueous solution in step d) further comprises a water
30 soluble polymer in an amount of 0.1-10% based on the weight of the mixture of particles of the calcium source, the phosphate source and the carbonate source.

40. The process according to claim 21, wherein step a) further comprises mixing a biocompatible polymer with said particles of the calcium source and the phosphate source in an amount of 0.5-30% based on the total weight of said particles in said non-aqueous liquid medium, wherein said biocompatible
5 polymer is soluble in said non-aqueous liquid medium, so that said porous apatite grains formed in step e) are bound by said biocompatible polymer to form a microspherical composite having a size of 0.5-1000 μm .

41. The process according to claim 40, wherein said said biocompatible
10 polymer is selected from the group consisting of polylactic acid, polyglycolic acid, poly(lactic-co-glycolic acid), polyanhydrides, polyethylene glycol, polyethylene oxide, polyacrylates, polymethacrylates, dextran, polysaccharides, hyaluronic acid, and mixture thereof.

42. The process according to claim 41, wherein said biocompatible
15 polymer is polylactic acid, polyethylene glycol, or poly(lactic-co-glycolic acid).

43. The process according to claim 22, wherein step a) further comprises mixing a biocompatible polymer with said particles of the calcium source, the
20 phosphate source and the carbonate source in an amount of 0.5-30% based on the total weight of said particles in said non-aqueous liquid medium, wherein said biocompatible polymer is soluble in said non-aqueous liquid medium, so that said porous apatite grains formed in step e) are bound by said biocompatible polymer to form a microspherical composite having a size of 0.5-1000 μm .

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44. The process according to claim 21 further comprising f) drying the porous apatite grains resulting from step e).

45. The process according to claim 21, wherein said drug in step b) and
30 said drug in step d) are a peptide, protein, enzyme, DNA, RNA, nutrient supplement agent, anti-inflammatory drug, anti-biotic drug, anti-histamine drug, anti-bacterial drug, anti-fungal drug, decongestant, anti-depressant,

anti-psychotic drug, anti-viral drug, anti-oncolytic drug, vaccine, anti-epileptic drug, anti-asthma drug, antioxidant or extract of herb.

46. The pharmaceutical dosage form according to claim 21, wherein said
5 drug in the aqueous solution in step d) is zinc gluconate, copper gluconate, salts of zinc, salts of copper, salts of iron, ascorbic acid, peptide, protein, enzyme, DNA, RNA, nutrient supplement agent, anti-inflammatory drug, anti-biotic drug, anti-histamine drug, anti-bacterial drug, anti-fungal drug, decongestant, anti-depressant, anti-psychotic drug, anti-viral drug, anti-oncolytic drug, vaccine,
10 anti-epileptic drug, anti-asthma drug, antioxidant, water soluble vitamins or extract of herb.

47. The pharmaceutical dosage form according to claim 21, wherein said
drug soluble in the non-aqueous liquid medium in step b) is ibuprophen, aspirin,
15 nutrient supplement agent, anti-inflammatory drug, anti-biotic drug, anti-histamine drug, anti-bacterial drug, anti-fungal drug, decongestant, anti-depressant, anti-psychotic drug, anti-viral drug, anti-oncolytic drug, anti-epileptic drug, anti-asthma drug, antioxidant, oil-soluble vitamins or extract of herb.

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48. A process for preparing a pharmaceutical dosage form comprising the following steps:

A) mixing particles of a calcium source and particles of a phosphate source in a non-aqueous liquid medium, and optionally milling the resulting
25 mixture, so that a slurry has a Ca/P ratio of 1.1-2.1 and particles suspended therein having a size of 0.01-100 μm ;

B) granulating the slurry;

C) adding an aqueous solution to the resulting granules from step B);

D) stirring or fluidizing the wetted granules, so that porous apatite grains
30 are formed, wherein said grains has a size of 0.1-1000 μm and said pores of said grain have an opening of 0.5-300 nm;

E) adding a drug in the form of a solution to the porous apatite grains from step D); and

F) drying the solution in step E), so that said drug is entrapped in pores of said grains.

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49. The process according to claim 48, wherein step A) further comprises mixing particles of carbonate source together with said particles of calcium source and phosphate source in an amount of 0.1-40% based on the total weight of said particles of calcium source and phosphate source.

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50. The process according to claim 48, wherein said non-aqueous liquid medium in step A) selected from the group consisting of methanol, ethanol, 1-propanol, 2-propanol, acetone, methyl ethyl ketone, toluene, ethyl acetate, butyl acetate, and a mixture thereof.

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51. The process according to claim 48, wherein said phosphate source in step A) is selected from the group consisting of magnesium phosphate, monocalcium phosphate anhydrate, dicalcium phosphate anhydrate, tricalcium phosphate, potassium dihydrogen phosphate, sodium dihydrogen phosphate, and a combination thereof.

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52. The process according to claim 48, wherein said calcium source in step A) is selected from the group consisting of calcium hydroxide, calcium chloride, calcium carbonate, and a combination thereof.

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53. The process according to claim 49, wherein said carbonate source in step A) is selected from the group consisting of calcium bicarbonate or sodium bicarbonate or potassium bicarbonate, and a combination thereof.

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54. The process according to claim 48, wherein the mixture of particles of the calcium source and the phosphate source has a Ca to P molar ratio of 1.1 to 2.1.

55. The process according to claim 54, wherein the mixture of particles of the calcium source and the phosphate source has a Ca to P molar ratio of 1.3 to 1.60.

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56. The process according to claim 49, wherein the mixture of particles of the calcium source and the phosphate source has a Ca to P molar ratio of 1.3 to 1.60.

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57. The process according to claim 48, wherein said granulating in step B) comprises atomizing said slurry and drying the resulting aerosol.

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58. The process according to claim 48, wherein said aqueous solution in step C) is sprayed to the resulting granules from step B), while stirring or fluidizing.

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59. The process according to claim 58, wherein said aqueous solution in step C) is water, phosphate buffered aqueous solution, or HanK's solution.

60. The process according to claim 48, wherein water contained in said aqueous solution in step C) added to the resulting granules from step B) is in a weight ratio of said water to the mixture of particles of the calcium source and the phosphate source of 0.05:1 to 0.30:1.

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61. The process according to claim 49, wherein water contained in said aqueous solution in step C) added to the resulting granules from step B) is in a weight ratio of said water to said mixture of particles of calcium source, phosphate source and carbonate source of 0.05:1 to 0.30:1.

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62. The process according to claim 48, wherein said aqueous solution in step C) further comprises a water soluble polymer in an amount of 0.1-10%

based on the weight of the mixture of particles of the calcium source and the phosphate source.

63. The process according to claim 62, wherein said water soluble
5 polymer is selected from the group consisting of chitosan, gelatin, agar, cellulose, chitin, starch, dextrin, cyclodextrin, polylactic acid, polyamino acid, polyethylene glycol, polyacrylates, hyaluronic acid, polyvinyl alcohol, povidone and mixture thereof.

10 64. The process according to claim 63, wherein said water soluble polymer is cellulose, polyethylene glycol, polyvinyl alcohol, or povidone.

65. The process according to claim 49, wherein said aqueous solution in
step C) further comprises a water soluble polymer in an amount of 0.1-10%
15 based on the weight of the mixture of particles of the calcium source, the phosphate source and the carbonate source.

66. The process according to claim 48, wherein step A) further comprises
mixing a biocompatible polymer with said particles of the calcium source and the
20 phosphate source in an amount of 0.5-30% based on the total weight of said particles in said non-aqueous liquid medium, wherein said biocompatible polymer is soluble in said non-aqueous liquid medium, so that said porous apatite grains formed in step D) are bound by said biocompatible polymer to
form a microspherical composite having a size of 0.5-1000 μm .

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67. The process according to claim 66, wherein said said biocompatible
polymer is selected from the group consisting of polylactic acid, polyglycolic acid,
poly(lactic-co-glycolic acid), polyanhydrides, polyethylene glycol, polyethylene
oxide, polyacrylates, polymethacrylates, dextran, polysaccharides, hyaluronic
30 acid, and mixture thereof.

68. The process according to claim 67, wherein said biocompatible polymer is polylactic acid, polyethylene glycol, or poly(lactic-co-glycolic acid).

69. The process according to claim 49, wherein step A) further comprises
5 mixing a biocompatible polymer with said particles of the calcium source, the phosphate source and the carbonate source in an amount of 0.5-30% based on the total weight of said particles in said non-aqueous liquid medium, wherein said biocompatible polymer is soluble in said non-aqueous liquid medium, so that said porous apatite grains formed in step D) are bound by said biocompatible
10 polymer to form a microspherical composite having a size of 0.5-1000 μm .

70. The process according to claim 48 further comprising D') drying the porous apatite grains resulting from step D).

71. The process according to claim 48, wherein said drug in step E) is a
15 peptide, protein, enzyme, DNA, RNA, nutrient supplement agent, anti-inflammatory drug, anti-biotic drug, anti-histamine drug, anti-bacterial drug, anti-fungal drug, decongestant, anti-depressant, anti-psychotic drug, anti-viral drug, anti-oncolytic drug, vaccine, anti-epileptic drug, anti-asthma drug,
20 antioxidant or extract of herb.